

Comparison of adefovir dipivoxil and pegylated interferon alpha-2a treatment in chronic hepatitis B patients

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ABSTRACT

OBJECTIVE: In this study, we aimed to evaluate the efficacy of pegylated interferon alpha 2a and adefovir dipivoxil treatment in chronic hepatitis B patients.

METHODS: This study was performed on patients treated for chronic hepatitis B in the Infectious Disease Clinic of Eskisehir Osmangazi University between 01.09.2005 and 31.03.2008. A total of 30 patients aged between 18 and 65 years constituted the study group. One of patient groups received (10 HBeAg negative, 4 HBeAg positive) PEG-IFN alpha 2a at a dose of 180 µg/once a week, whereas the other group (11 HBeAg negative, 5 HBeAg positive) received daily oral doses of 10 mg ADV. Treatment responses were evaluated at week 48.

RESULTS: Reductions in serum HBV DNA levels at the end of 48 weeks were 4.8 log₁₀ copy/ml and 4.2 log₁₀ copy/ml in HBeAg negative patients who received ADV or PEG-IFN alpha 2a, , respectively. Biochemical response rates were 60% and 91% in PEG-IFN alpha 2a and ADV groups, respectively. Among HBeAg positive patients, reductions in serum HBV DNA levels were 3. 2 log₁₀ copy/ml and 4 log₁₀ copy/ml in ADV and PEG-IFN alpha 2a groups, at week 48, respectively. Biochemical response rates were 50% and 40% in PEG-IFN alpha 2a and ADV groups, respectively. No significant difference was determined in biochemical and virological responses in HBeAg positive and negative patients between PEG-IFN alpha 2a and ADV groups, at week 48. When both treatment groups were evaluated for side effects, it was observed that side effects were significantly common in PEG-IFN alpha 2a group.

CONCLUSION: When we compared PEG-IFN alpha 2a and ADV treatment in both HBeAg positive and negative patients, biochemical and virological response rates at 48 weeks were similar.

Key words: Adefovir dipivoxil, chronic hepatitis B, pegylated interferon alpha 2a



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Nearly 350 million people in the world have been estimated to contract chronic hepatitis B (CHB). Chronic hepatitis B patients have a higher risk of developing cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC) [1]. Every year nearly one million people die from end-stage hepatic failure, and eventually 5-10% of them require liver transplantation [2]. Effective treatment modalities are needed to prevent progression of CHB to HCC, and death [3]. Therapeutic targets include suppression of the HBV replication, histopathological recovery of the liver, eradication of HBV, prevention of cirrhosis, and HCC, and prolongation of life span [4].

Currently, drugs used in the treatment of CHB are conventional interferon-alpha, pegylated interferon-alpha (PEG-IFN α -2a and α -2b), lamivudine, telbivudine, emtricitabine, entecavir, adefovir dipivoxil (ADV), and tenofovir [2].

Interferons (IFNs) have antiviral, antiproliferative, and immunomodulator effects. Because of short half-lives of classical interferons, fluctuations in blood levels of these drugs can be seen which decrease antiviral efficacy of them. Side effects are more frequently seen when conventional interferons reach to their peak serum levels. To preclude these disadvantages polyethylene glycol molecules were added to interferons, and pegylated interferons have been obtained. Thus, half-lives of interferons are prolonged, and once weekly doses have ensured sustained antiviral response [5, 6].

Non-interferon treatment alternatives of CHB include nucleotide analogues. Adefovir, is a pro-drug of ADV. Adefovir is a acyclic nucleotide analogue of adenosine diphosphate [7]. Adefovir is phosphorylated to its active metabolite adenosine diphosphate by cellular kinases. Following entry of adefovir diphosphate into viral DNA, it depletes DNA with resultant inhibition of HBV DNA polymerase. It is a weak inhibitor of human DNA polymerases [8].

This study was planned to compare therapeutic effectiveness of 48 weeks of ADV, and PEG-IFN α -2a therapies in CHB patients followed up in clinics of infectious diseases of our university hospital.

MATERIALS AND METHODS

A total of 30 patients (HBeAg negative, n=21, and HBeAg positive, n=9) who were followed up in the Department of Infectious Diseases of our University hospital between 09.01. 2005, and 03.31. 2008 were included in the study. Approval of the Ethics Committee of our University was obtained. All patients were informed about the study, and they were enrolled in the study after receipt of their written informed consent.

Inclusion criteria:

- Male, and female patients aged between 18-65 years whose HbsAg positive status lasted for more than 6 months,
- HBeAg-negative CHB patients with HBV DNA levels over 10^4 copies/ml, and elevated (1.3-10 ULN) or normal (0-40 IU/L) alanine aminotransferase (ALT) levels
- HBeAg-positive CHB patients with HBV DNA values over 10^5 copies/ml together with elevated or normal ALT levels,
- Previously untreated patients or those with post-treatment recurrences (cases who received last dose of treatment 6 months ago)

Exclusion criteria:

- Patients who received CHB treatment within the previous 6 months, those with hepatitis A, C or D or HIV co-infection, pregnancy, autoimmune disease, malignancy, decompensated liver disease, metabolic liver disease, severe psychiatric disease, serious cardiac, and pulmonary diseases, decreased Hb values (<12 g/dl in female, and <13 g/dl in male patients), lower neutrophil counts (<1500/mm³), and increased (>1.5 mg/dl) creatinine levels.

Patients who met inclusion criteria underwent liver biopsy, and patients with biopsy-proven chronic liver disease were divided into 2 groups. One of these groups received weekly subcutaneous doses of 180 μ g PEG-IFN α -2a, while the other group was treated with daily oral doses of 10 mg ADV. Evaluation period was determined as 48 weeks. Patients who received pegylated interferon were monitored at the second weeks of treatment after at the end of the

first month of the treatment, and then at 4-weekly intervals. In the ADV group, the first follow-up visit was performed at the end of the first month, after at the third months of treatment and then at 3-monthly intervals. Serum HBV DNA levels were measured using Corbett Real Time PCR method (viral load detection range of the device: 10^2 - 10^{11}). Evaluation of the treatment modalities: Decrease in serum HBV DNA levels down to undetectable levels at the end of 48. weeks as measured with PCR method was evaluated as virological response. However, regression of ALT levels down to normal limits was considered as biochemical response. In HBeAg-positive patients, clearance of HBeAg, and anti-Hbe positivity were evaluated as HBeAg seroconversion.

For statistical analysis, SPSS 13.0, and Sigmatat package programs were used. In statistical analysis, normality tests, frequency tables, T-test, Mann Whitney U-test, two way repeated measures ANOVA, and chi-square tests were used. $P < 0.05$ was considered as the level of statistical significance.

RESULTS

Study population consisted of 11 female (36.6%), and 19 male (63.4%) patients. Baseline characteristics of HBeAg-positive, and negative patients are seen in Table 1.

Any difference was not detected between groups of patients who received PEG-IFN α -2a or ADV as for reduction in HBV DNA values at the end of 12., 24., and 48. weeks ($p > 0.05$) (Table 2). A significant difference was not detected among HBeAg –positive, and HbeAg-negative patients in the PEG-IFN α -2a and ADV groups with respect to biochemical, and virological response rates ($p > 0.05$) (Table 3). HBeAg negativity was achieved in one patient in both PEG-IFN α -2a, and ADV groups.

During the treatment process of the patients who received PEG-IFN α -2a, side effects such as fever, headache, dizziness, lassitude, myalgia, nausea, abdominal pain, dry mouth, nosebleed, pruritus, dry skin, and itching, reaction at the injection site, hair loss, weight loss, loss of appetite, irritability, and insomnia were seen. However, neutropenia, thrombocytopenia, and thyroid dysfunction were the most frequently detected laboratory abnormalities. Dose modifications were made in 42.8% of the patients who received PEG-IFN, and treatment of none of these patients was prematurely terminated because of development of side effects. Emergence of neutropenia, and thrombocytopenia required dose reduction in 28.5, and 14.3% of the patients who received PEG-IFN, respectively. (Table 4). However in the ADV treatment group, most frequently seen side effects were headache ($n=3$; 18.7%), abdominal

TABLE 1. Baseline characteristics of the patients

Characteristics	HBeAg (-)			HBeAg (+)		
	†PEG-IFN alpha 2a	‡ADV	p	PEG-IFN alpha 2a	ADV	p
Age (years)	33.2±10.3	43.2±9.3	<0.05	28.7±9.9	30.6±5.9	>0.05
Gender						
Female	2 (20%)	5 (45.5%)	>0.05	–	4 (80%)	<0.05
Male	8 (80%)	6 (54.5%)		4 (100%)	1 (20%)	
ALT*	126.70±177.24	89.18±77.73	>0.05	254.75±128.26	148.8±171.30	>0.05
HBV DNA (log 10 copies/ml)*	5.36±0.72	6.39±1.67	>0.05	7.3±1.2	6.9±1.2	>0.05
Fibrosis*	1.50±0.85	2±1.09	>0.05	2.25±0.95	1.80±1.3	>0.05

*Mean±SD; †PEG-IFN alpha 2a, pegylated interferon-alpha 2a; ‡ADV, adefovir dipivoxil.

TABLE 2. Mean HBV DNA values at certain time points of PEG-IFN alpha 2a, and ADV treatment in patients with HBeAg negative, and positive patients

HBV DNA (10 log copies/ml) *	HBeAg (-)			HBeAg (+)		
	†PEG-IFN alpha-2a	‡ADV	p	†PEG-IFN alpha-2a	‡ADV	p
Onset of treatment	5.3±0.7	6.3±1.6	>0.05	7.39±1.21	6.9±1.2	>0.05
12. weeks	1.1±1.2	2.2±2.4	>0.05	3.3±3.0	5.1±2.7	>0.05
24. weeks	1.1±1.1	1.6±2.2	>0.05	3.5±2.2	4.2±3.9	>0.05
48. weeks	1.1±1.8	1.5±1.8	>0.05	3.3±2.7	3.7±3.4	>0.05

*Mean±SD; †PEG-IFN alpha 2a, pegylated interferon-alpha 2a; ‡ADV, adefovir dipivoxil.

TABLE 3. Biochemical, and virological response rates (n, %) obtained with PEG-IFN α-2a, and ADV treatments

Characteristics	HBeAg (-)			HBeAg (+)		
	†PEG-IFN alpha-2a	‡ADV	p	PEG-IFN alpha-2a	ADV	p
Biochemical responses, n	6 (60%)	10 (91%)	>0.05	2 (50%)	2 (40%)	>0.05
Virological responses, n	9 (90%)	9 (82%)	>0.05	1 (25%)	2 (40%)	>0.05

*PEG-IFN alpha 2a, pegylated interferon-alpha 2a; ‡ADV, adefovir dipivoxil.

pain (n=2; 12.5%), and dyspepsia (n=2; 12.5%). In none of the patients in the ADV group increase in serum creatinine values, and alterations in serum phosphorus levels were seen.

DISCUSSION

PEG-IFN α-2a, and ADV are among recommended treatment modalities for CHB both in national, and international consensus reports [2, 4, 9, 10].

In the evaluation of treatment response in CHB, normalization of serum ALT levels, decrease in serum HBV DNA levels, loss of HBeAg in HBeAg positive patients, and improvement in histopathological markers of CHB are taken into consideration. Endpoints for CHB are normalization of ALT, suppression of HBV DNA to undetectable

levels, loss or seroconversion of HBeAg in HBeAg positive patients, and improvement in histopathological markers of CHB [11, 12].

In the treatment, decrease in HBV DNA levels is important as for the suppression of viral replication. In HBeAg negative patients, Marcellin et al. detected a decrease of 4.1 log copies/ml in the level of HBV DNA, at the end of the treatment with PEG-IFN α-2a, while Hadziyannis et al. revealed a decrease of 3.91 log copies/ml in the level of HBV DNA following 48 weeks of treatment with ADV. [13, 14]. In our study, decreases in the mean HBV DNA values were detected at the end of 48 weeks in the group of patients who received PEG-IFN α-2a or ADV (at levels of 4.2, and 4.8 log copies/ml, respectively). A statistically significant difference was not found between both groups as for decreases in

TABLE 4. Most frequently seen side effects during pegylated interferon alpha 2 a treatment in HBeAg positive, and negative patients

Side effect	n	%	Side effect	n	%
Fever	13	92.9	Dry skin, itching	10	71.4
Weight loss	13	92.9	Nosebleed	9	64.3
Headache	10	71.4	Injection site reaction	3	21.4
Hair loss	9	64.3	Loss of appetite	4	28.6
Lassitude	12	85.7	Thyroid dysfunction	3	21.4
Muscle pain	12	85.7	Neutropenia	13	93
Abdominal pain	4	28.6	Thrombocytopenia	10	71.4
Dry mouth	6	42.9	Change in dosage, because of	6	42.8
			Leukopenia	4	28.5
			Thrombocytopenia	2	14.3

HBV DNA values at the end of 48 weeks ($p>0.05$).

Cooksley et al. and also Caruntu et al. detected decreases in post-treatment HBV DNA levels in HBeAg positive patients who received PEG-IFN α -2a (decreases of 3.5, and 3 log copies/ml, respectively [15, 16]. Marcellin et al. detected a decrease in HBV DNA levels at a rate of 3.5 log copies/ml, and Zeng et al. disclosed a drop of 4.2 log copies/ml in HBeAg positive patients who received ADV [17, 18]. In our patients who received PEG-IFN α -2a, HBV DNA levels decreased down to 4 log copies/ml, while in the ADV group a decrease in HBV DNA levels was at a rate of 3.2 log copies/ml at the end of 48 weeks. A significant difference couldn't be found between both groups as for decrease in HBV DNA values at the end of 48 weeks ($p>0.05$).

Marcellin et al. detected end-treatment virological response (HBV DNA <400 copies/ml) rates in HBeAg- negative patients who received PEG-IFN α -2a (63%), PEG-IFN –LAM combination (87%) or LAM (73%), as indicated in parentheses [13]. Hadziyannis et al. reported median virological response rate of 51% in HBeAg negative patients under ADV treatment at the end of 48 weeks [14]. Virological response rates in patients who received PEG-IFN α -2a or ADV were 90, and 82% at the end of 48 weeks, respectively. A significant difference could not be found as for virological response

rates as assessed at the end of 48 weeks ($p>0.05$).

Lau et al. had detected end-treatment virological response rates (HBV DNA <400 copies/ml) in HBeAg positive patients who received PEG-IFN α -2a (25%), pegylated interferon alpha-LAM combination (69%), and LAM (40%) as indicated in parentheses [3]. Cooksley et al. noted end-treatment virological response rate in the PEG-IFN α -2a group as 39 percent. While, Marcellin et al. revealed a 21% virological response rate in HBeAg positive patients who received ADV [15, 17]. In a study performed in our country, end-treatment virological response rate (HBV DNA <400 copies/ml) was detected as 33.3% in HBeAg positive patients who received PEG-IFN α -2a [19]. Virological response rates at the end of 48 weeks in our patients who received PEG-IFN α -2a or ADV were found to be 25, and 40%, respectively. A significant difference was not noted between both treatment groups as for virological response rates at the end of 48 weeks ($p>0.05$).

Another parametre indicative of treatment response, at the end of the treatment is normalization of ALT levels. Different ALT normalization rates were detected in HBeAg positive patients who received PEG-IFN α -2a (Lau et al., 41%) or ADV (Marcellin et al., 48%) [3, 17]. In our HBeAg positive patients end-treatment ALT normalization rates were 40% in the ADV, and 50% in the PEG-

IFN α -2a groups. A significant intergroup difference could not be found as for mean ALT normalization rates at the end of 48 weeks ($p > 0.05$).

Post-treatment ALT normalization rates were found to be 59%, and 77% in HBeAg negative patients treated with PEG-IFN α -2a (Marcellin et al.) or ADV (Hadziyannis et al.), respectively [13,14]. In a study performed in our country by Karabay et al., post-treatment biochemical response rate in HBeAg negative patients receiving PEG-IFN α -2a was detected to be 37.1 percent [20]. ALT normalization rates in our HBeAg negative patients receiving PEG-IFN α -2a or ADV were 60, and 91%, respectively. At the end of 48 weeks, both groups did not differ as for biochemical response rates ($p > 0.05$).

Dogan et al. couldn't detect HBeAg seroconversion at the end of 48 weeks in HBeAg positive patients who received PEG-IFN α -2a [19]. In our study, HBeAg negativity was achieved in one patient in both HBeAg treatment groups, without any significant intergroup difference ($p > 0.05$). HBeAg seroconversion was not observed in both groups. However because of scarcity of our patient population, larger scale studies should be performed for the evaluation of this issue.

Most frequently seen side effects in our PEG-IFN α -2a group were fever, myalgia, lassitude, weight loss, skin itching, and dryness, nosebleed, headache, hair loss, and dry mouth, However in our ADV group mostly seen side effects were abdominal pain, headache, and dyspepsia. Our results related to side effects were in accordance with those of the other studies [13, 14, 15, 21, 22, 23, 24, 25]. Remarkably, greater number of side effects were seen in the PEG-IFN α -2a group relative to the ADV group.

In 42.8% of our patients who received PEG-IFN α -2a, treatment dose was changed. Most frequent causes of dose alterations were neutropenia, and thrombocytopenia. These results were in accordance with those of the other studies [5, 13]. In the PEG-IFN α -2a group dose alterations were required because of development of side effects, however in our ADV group dose modifications were not

necessitated. In both groups, any condition which required discontinuation of treatment because of side effects was not encountered.

In conclusion, 48 weeks of PEG-IFN α -2a, and ADV treatments in both HBeAg positive, and negative patients are not superior to each other with respect to biochemical, and virological response rates. When these medications were evaluated as for side effects developing during treatments, PEG-IFN α -2a therapy adversely effected quality of life of the patients more frequently. Evaluation of sustained viral response is important in the selection of treatment modality. Lack of any parameters which allow us to evaluate sustained viral, and histological response suggests the need for long-term studies which would evaluate therapeutic efficacy.

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